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## ORIGINAL ARTICLE

# Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study

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**Background:** Cabozantinib, an orally bioavailable inhibitor of tyrosine kinases including MET, AXL, and VEGF receptors, was assessed in patients with hepatocellular carcinoma (HCC) as part of a phase 2 randomized discontinuation trial with nine tumor-type cohorts.

**Patients and methods:** Eligible patients had Child-Pugh A liver function and  $\leq 1$  prior systemic anticancer regimen, completed  $\geq 4$  weeks before study entry. The cabozantinib starting dose was 100 mg daily. After an initial 12-week cabozantinib treatment period, patients with stable disease (SD) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 were randomized to cabozantinib or placebo. The primary endpoint of the lead-in stage was objective response rate (ORR) at week 12, and the primary endpoint of the randomized stage was progression-free survival (PFS).

**Results:** Among the 41 HCC patients enrolled, the week 12 ORR was 5%, with 2 patients achieving a confirmed partial response (PR). The week 12 disease control rate (PR or SD) was 66% (Asian subgroup: 73%). Of patients with  $\geq 1$  post-baseline scan, 78% had tumor regression, with no apparent relationship to prior sorafenib therapy. Alpha-fetoprotein (AFP) response ( $>50\%$  reduction from baseline) occurred in 9 of the 26 (35%) patients with elevated baseline AFP and  $\geq 1$  post-baseline measurement. Twenty-two patients with SD at week 12 were randomized. Median PFS after randomization was 2.5 months with cabozantinib and 1.4 months with placebo, although this difference was not statistically significant. Median PFS and overall survival from Day 1 in all patients were 5.2 and 11.5 months, respectively. The most common grade 3/4 adverse events, regardless of attribution, were diarrhea (20%), hand-foot syndrome (15%), and thrombocytopenia (15%). Dose reductions were utilized in 59% of patients.

**Conclusions:** Cabozantinib has clinical activity in HCC patients, including objective tumor responses, disease stabilization, and reductions in AFP. Adverse events were managed with dose reductions.

**Trial registration number:** NCT00940225.

**Key words:** hepatocellular carcinoma, cabozantinib, vascular endothelial growth factor receptor, progression-free survival, overall survival, tumor response

## Introduction

The receptor tyrosine kinase MET and its ligand, hepatocyte growth factor, play important roles in diverse aspects of tumor

pathobiology, including tumor growth, survival, neoangiogenesis, invasion, and dissemination [1]. MET pathway activation and dysregulation have been implicated in multiple cancers, including hepatocellular carcinoma (HCC) [1, 2], and may play

a role in resistance to antiangiogenic therapy [3–6]. Similarly, increased expression of the receptor tyrosine kinase AXL has also been reported in HCC and may promote invasive behavior [7]. In other settings AXL signaling has been linked to resistance to VEGF receptor (VEGFR) inhibitors [6]. VEGFRs and their ligands are central mediators of tumor neoangiogenesis and lymphangiogenesis [8]. High VEGF levels in both tissue and serum predict poor disease-free and overall survival (OS) in HCC [9].

Currently, the only approved systemic therapy for HCC is sorafenib, an inhibitor of VEGFRs, RAF, and other protein kinases, which provides a modest survival benefit for patients with unresectable disease [10]. Other molecularly targeted agents including several antiangiogenics have failed to prolong survival in phase 3 trials as either first-line therapy compared with sorafenib (sunitinib, brivanib, linifanib, erlotinib plus sorafenib) or second-line therapy following failure of sorafenib (brivanib, everolimus, ramucirumab) [11]. Agents currently in phase 3 trials include lenvatinib and nivolumab as first-line treatments and tivantinib and regorafenib as second-line treatments [12, 13]. Recently, regorafenib has shown a survival benefit compared with placebo in this setting with median OS of 10.6 vs 7.8 months [12]. In a phase 1/2 trial, the immune checkpoint inhibitor nivolumab demonstrated a 67% disease control rate including two complete responses (5%) and 6 month overall survival rate of 72% [13].

Cabozantinib (XL184), an orally bioavailable tyrosine kinase inhibitor (TKI), targets multiple receptor tyrosine kinases, including VEGFRs, MET, AXL, RET, KIT, and FLT3. In xenograft models, cabozantinib treatment suppressed MET and VEGFR2 signaling, rapidly induced apoptosis of endothelial and tumor cells, and resulted in tumor regression [14]. In addition, cabozantinib treatment suppressed HCC tumor growth and metastasis in a mouse xenograft model [15], and prolonged survival in a MET-driven transgenic mouse model of HCC (D. Yang, J.M. Bishop, personal communication, August 2010).

In a phase 1 trial, cabozantinib treatment resulted in tumor regression in multiple cancer types [16]. In phase 3 trials cabozantinib significantly improved PFS and objective response rate (ORR) compared with placebo in patients with progressive metastatic medullary thyroid cancer and significantly improved PFS, ORR, and OS compared with everolimus in patients with advanced renal cell carcinoma (RCC) previously treated with a VEGFR TKI [17, 18].

Based on cabozantinib's broad clinical activity in multiple tumor types seen in an earlier phase 1 study [16], a phase 2 randomized discontinuation trial (RDT) was conducted in nine tumor types, including HCC (NCT00940225) [19]. This report describes results from the HCC cohort of the phase 2 RDT.

## Patients and methods

### Patients

Eligible patients had HCC diagnosed by core biopsy or appropriate imaging technique [computed tomography (CT) or magnetic resonance imaging (MRI)], measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 with protocol-defined modifications [20], and, unless newly diagnosed and never treated, evidence of progressive disease (PD) by

CT, MRI, or bone scan at screening. Additional inclusion/exclusion criteria have been previously described (see [supplementary Patients and Methods](#), available at *Annals of Oncology* online) [21].

### Study design

All patients received cabozantinib at a starting dose of 100 mg daily during a 12-week lead-in phase. At week 12, patients with SD were randomized to cabozantinib or placebo, patients with a PR could continue open-label cabozantinib treatment, and patients with PD at or before week 12 discontinued treatment. See [supplementary Figure S1](#), available at *Annals of Oncology* online for additional study design details.

The primary endpoint of the lead-in phase was ORR at week 12, and the primary endpoint of the randomized phase was PFS. Secondary endpoints included safety, tolerability, and PFS and OS of the entire cabozantinib-treated population. An additional exploratory endpoint was assessment of changes in serum alpha-fetoprotein (AFP).

### Study assessments

Efficacy assessments included radiographic soft-tissue imaging with CT and/or MRI of the chest/abdomen with investigator-assessed response using RECIST 1.0. Other clinical assessments included medical and cancer history, physical examination, vital signs, body weight, electrocardiography, Eastern Cooperative Oncology Group (ECOG) performance status, safety laboratory values (serum chemistry, hematology, coagulation, and urinalysis), concomitant medications, adverse events (AEs), and information on subsequent anti-cancer treatment. Pre-dose pharmacokinetic (PK) blood samples were collected at baseline and after 6 and 12 weeks for determining plasma cabozantinib concentrations, with additional week 2 and 4 assessments in some patients.

### Study oversight

A study oversight committee monitored efficacy during lead-in, and an independent data monitoring committee reviewed safety during the blinded randomized stage. The study oversight committee was empowered to suspend randomization by cohort based on data review.

### Statistical considerations

Statistical considerations for this RDT have been previously described (see [supplementary Patients and Methods](#), available at *Annals of Oncology* online) [21].

## Results

### Patient characteristics and disposition

The RDT enrolled 526 patients across nine tumor-type cohorts. Results from 41 patients with HCC enrolled from the United States, Belgium, and Taiwan are presented. Median follow-up was 19.4 months. Baseline demographic and clinical characteristics are summarized in Table 1. Thirty-two patients had  $\geq 1$  line of prior systemic anticancer therapy; of these, 24 had prior TKIs (including sorafenib in 22 patients). Among the 41 patients enrolled to receive open-label cabozantinib during the 12-week lead-in, 12 discontinued study treatment before week 12, seven continued open-label cabozantinib after week 12, and 22 were randomized to receive cabozantinib ( $n = 10$ ) or placebo ( $n = 12$ ). See [supplementary Figure S2](#), available at *Annals of Oncology* online for additional details of patient disposition. The data cutoff date for the results presented in this publication was December 16, 2011.

**Table 1. Baseline demographic and clinical characteristics of HCC patients**

Characteristic	Entire treated population (n = 41) Patients, n (%)
Age (years)	
Median (range)	60 (32–82)
Sex	
Male	31 (76)
Female	10 (24)
Race	
Asian	15 (37)
Non-Asian	26 (63)
ECOG performance status	
0	18 (44)
1	23 (56)
Etiology of disease	
Hepatitis B	10 (24)
Hepatitis C <sup>a</sup>	10 (24)
Alcohol-related	6 (15)
Other/unknown	15 (37)
Measurable disease	41 (100)
Extrahepatic spread	30 (73)
Hypersplenic/cytopenic	
Hemoglobin <11 g/dL	16 (39)
Thrombocytopenia	16 (39)
AFP (ng/ml)	
Median (range)	368 (3–259, 298)
Prior lines of systemic therapy	
0	9 (22)
1	30 (73)
2	2 (5)
Prior anticancer therapy	
Tyrosine kinase inhibitor	24 (59)
Sorafenib	22 (54)
Surgical resection	17 (42)
Locoregional therapy <sup>b</sup>	21 (51)

AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group.

<sup>a</sup>Two hepatitis C patients also had alcohol-related etiology.

<sup>b</sup>Locoregional therapy includes transarterial embolization, percutaneous ethanol injection radiofrequency ablation, and radiotherapy applied to extrahepatic metastatic lesions.

While the goal of the study was to randomize approximately 70 patients per cohort (see [supplementary Patients and Methods](#), available at *Annals of Oncology* online), randomization was halted early for all cohorts due to the high rates of tumor regression and the observation of symptomatic progression in individual patients randomized to placebo in several of the disease cohorts [20].

## Tumor response

The primary endpoint for the open-label lead-in phase was ORR per RECIST 1.0 at week 12. Among 41 enrolled patients, two had a confirmed partial response (PR) at week 12, resulting in an ORR of 5%. Thirty-one patients had SD as a best response at week 6 and/or week 12 (SD), and three had PD (Table 2). Additionally,

**Table 2. Summary of week 12 response in HCC patients by RECIST 1.0 (n = 41)**

Parameter	Patients, n (%)
RECIST response	
Confirmed partial response	2 <sup>a</sup> (5)
Stable disease <sup>b</sup>	31 (76)
Progressive disease	3 (7)
Missing data	4 (10)
Unable to evaluate	1 (2)
Week 12 disease control <sup>c</sup>	27 (66)
AFP response evaluable <sup>d</sup>	26
>50% Decrease from baseline	9 (35)

AFP, alpha-fetoprotein; RECIST, Response Evaluation Criteria in Solid Tumors.

<sup>a</sup>In addition, one patient assessed with stable disease at week 12 and randomized to placebo had a confirmed partial response at week 18.

<sup>b</sup>Stable disease at week 6 and/or week 12.

<sup>c</sup>Disease control defined as confirmed partial response + stable disease at week 12.

<sup>d</sup>Baseline AFP  $\geq 20$  ng/ml.

one patient randomized to placebo at week 12 had a PR at week 18. The disease control rate (DCR: PR or SD) at week 12 was 66% overall (Table 2) and 73% (11 of 15) in Asian patients. Thirty-six assessable patients had  $\geq 1$  post-baseline assessment during the initial 12 weeks of therapy, and 28 (78%) of these patients had  $\geq 1$  scan demonstrating a reduction of measurable disease (Figure 1A). Nine of the 26 (35%) patients with  $\geq 1$  post-baseline measurement had AFP responses (defined as >50% reduction from baseline in patients with AFP >20 ng/ml at baseline; Figure 1B).

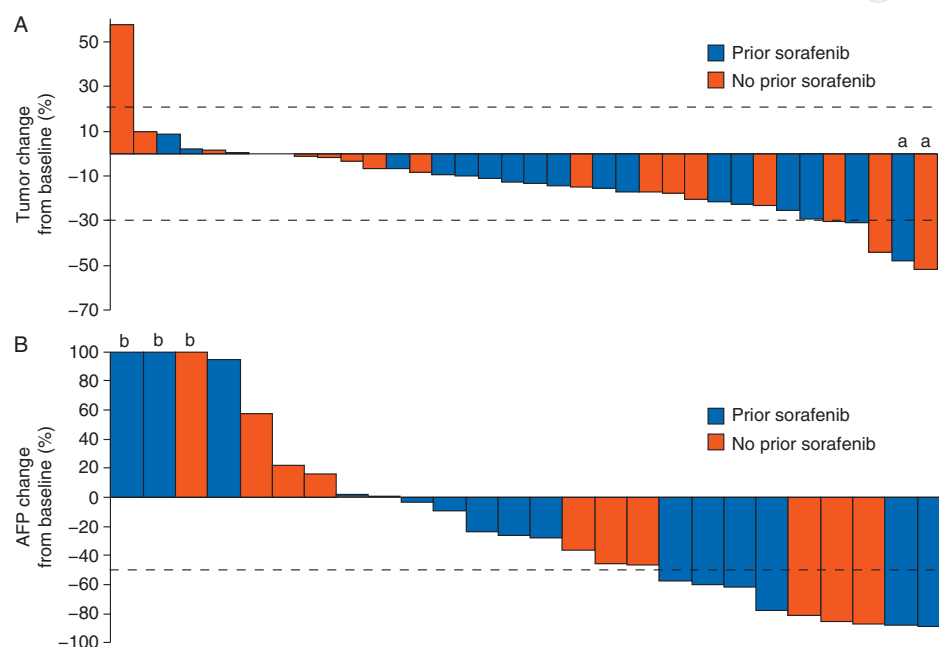
## Progression-free and overall survival

Among the patients who had SD at week 12 ( $n = 22$ ), 12 patients were randomized to placebo and 10 to cabozantinib. No significant difference in PFS was observed between the two groups. Median PFS from time of randomization was 2.5 months [95% confidence interval (CI), 1.3–6.8 months] for cabozantinib patients and 1.4 months (95% CI, 1.3–4.2 months) for placebo (data not shown).

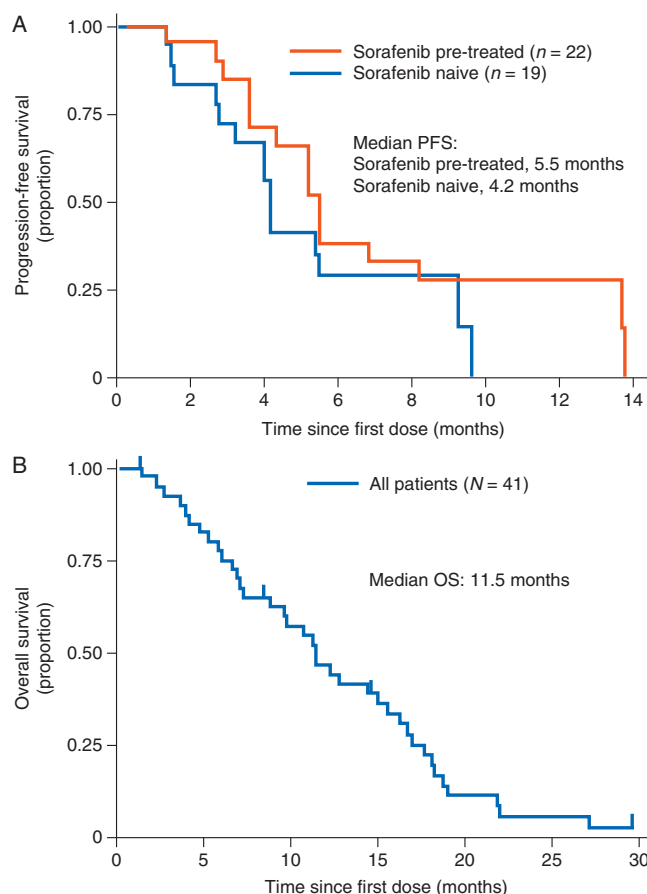
For the analysis of overall PFS from the first dose of cabozantinib, the piecewise estimation method described by Ratain et al. [22] was used (see [supplementary Patients and Methods](#), available at *Annals of Oncology* online). Median overall PFS for all 41 treated patients from the start of the study was 5.2 months (data not shown). Median overall PFS for sorafenib-pretreated ( $n = 22$ ) versus sorafenib-naïve ( $n = 19$ ) patients was 5.5 versus 4.2 months, respectively (Figure 2A), and 4.2 versus 5.5 months for Asian ( $n = 15$ ) versus non-Asian ( $n = 26$ ) patients, respectively (data not shown). Median OS for all 41 treated patients was 11.5 months (95% CI, 7.3–15.6 months; Figure 2B).

## Safety

Table 3 summarizes AEs reported during lead-in regardless of attribution. All patients had  $\geq 1$  AE; most experienced >1 event.



**Figure 1.** (A) Best change from baseline in investigator-assessed measurements of soft-tissue lesions using Response Evaluation Criteria in Solid Tumors (version 1.0) was determined for hepatocellular carcinoma (HCC) patients who had baseline and at least one post-baseline radiographic scan in the first 12 weeks ( $n = 36$ ). A reduction in the sum of measurable lesions was reported for 78% of assessable patients. Change in measurable disease was independent of prior treatment with sorafenib. (B) Best change from baseline in alpha-fetoprotein (AFP) measurements was determined for HCC patients who had baseline AFP  $\geq 20$  ng/ml ( $n = 26$ ). <sup>a</sup>Confirmed partial response. <sup>b</sup>Increase  $> 100\%$  from baseline.



**Figure 2.** Kaplan-Meier estimates of (A) progression-free survival (PFS) in all patients with HCC by sorafenib pretreatment status. (B) Overall survival (OS) for all patients with HCC.

**Table 3. Most frequently reported adverse events in HCC patients during lead-in stage regardless of causality**

Adverse event <sup>a</sup>	All grades (n = 41) Patients, n (%)	Grade ≥3 (n = 41)
Any adverse event	41 (100)	35 (85)
Diarrhea	26 (63)	8 (20)
Hand-foot syndrome	23 (56)	6 (15)
Fatigue	23 (56)	1 (2)
Thrombocytopenia	15 (37)	6 (15)
Nausea	15 (37)	1 (2)
Vomiting	15 (37)	1 (2)
Decreased appetite	12 (29)	0 (0)
Aspartate aminotransferase increased	11 (27)	4 (10)
Hypertension	10 (24)	4 (10)
Rash	10 (24)	0 (0)
Asthenia	9 (22)	3 (7)
Weight decreased	9 (22)	1 (2)
Constipation	9 (22)	0 (0)
Hair color changes	9 (22)	0 (0)

CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; MedDRA, Medical Dictionary for Regulatory Activities.

<sup>a</sup>MedDRA v. 14.1 Preferred Terms (converted to US spelling), CTCAE v. 3.0 grading.

The most common grade ≥3 AEs were diarrhea (20%), hand-foot syndrome (15%), thrombocytopenia (15%), hypertension (10%), and transaminase elevation (10%). There were no grade 5 AEs considered related to study treatment, and no clinically significant bleeding events were reported during the lead-in period. No patient discontinued study treatment due to an AE during the 12-week lead-in. Dose reductions were employed in 59% of patients. The median average daily dose was ~66 mg/day, and the median time to first dose reduction was 39.5 days.

## Pharmacokinetics

The pre-dose mean plasma concentration ( $\pm$  standard deviation) of cabozantinib was 861 ( $\pm$ 375) ng/ml with a corresponding percentage coefficient of variation of 43.6% in patients ( $n = 14$ ) who received at least 13 of 15 uninterrupted 100-mg/day cabozantinib doses over the 2 weeks before the PK sampling visit on week 6. Cabozantinib exposure in the HCC cohort of the RDT was similar to the other disease-specific cohorts in the study.

## Discussion

Cabozantinib inhibits targets considered important for HCC progression and resistance to first-line sorafenib therapy including VEGFRs, MET, and AXL. In this RDT, cabozantinib showed preliminary signs of clinical activity in both sorafenib-pretreated and sorafenib-naïve patients with advanced HCC.

In HCC patients, cabozantinib demonstrated a week 12 ORR of 5% by RECIST 1.0 and a week 12 DCR of 66%. During the lead-in phase, cabozantinib treatment resulted in a reduction in target lesions from baseline in 78% of assessable HCC patients. Cabozantinib activity in advanced HCC is further supported by the 35% of patients achieving >50% AFP reduction, as AFP response is associated with tumor response and survival across stages and treatment modalities in HCC [23–25].

In the randomized population, there was no significant difference in median PFS between the cabozantinib and placebo arms, although the trend favored PFS improvement in the cabozantinib arm. In the entire cabozantinib-treated population, median PFS was 5.2 months with similar results across multiple subsets including Asian versus non-Asian and sorafenib-pretreated versus sorafenib-naïve populations. Median OS for all cabozantinib-treated patients was 11.5 months (95% CI, 7.3–15.6 months).

The most frequent AEs in this cohort (e.g. diarrhea, weight loss, hand-foot syndrome) were mainly mild to moderate in severity and consistent with those observed in other cohorts and with sorafenib in HCC patients.

Mean steady-state pre-dose plasma cabozantinib concentration and variability were consistent with other cohorts and other cabozantinib studies, suggesting that cabozantinib plasma PK was not markedly altered in HCC patients. In a separate study of subjects with hepatic impairment, geometric least squared mean ratios for plasma cabozantinib AUC<sub>0-inf</sub> for impaired to normal organ function cohorts were ~81% and ~63% higher in subjects with mild and moderate hepatic impairment, respectively [26].

The RDT design allows assessment of clinical activity while minimizing exposure to placebo, creates a controlled trial without upfront randomization, and decreases the heterogeneity of the randomized population, thus increasing statistical power with fewer patients [22]. The goal of this study was to identify indications where cabozantinib exhibits disease stabilizing activity, however, the high rate of tumor regression found for several tumor types led to an early halt of the randomized phase of the study. Therefore, the targeted patient accrual was not met, and the full utility of the RDT trial design was not realized.

Based on these preliminary signs of clinical activity, a phase 3, randomized, double-blind, controlled trial has been initiated comparing cabozantinib to placebo in patients with HCC who have received prior sorafenib therapy (CELESTIAL; NCT01908426). Clinical development of cabozantinib for this patient population is also supported by preclinical studies in HCC models that demonstrate the importance of VEGFRs, MET, and AXL in tumor progression [2, 15] and MET in acquired resistance to anti-angiogenic therapy including sorafenib [3]. Furthermore, in patients with advanced RCC, cabozantinib was effective following treatment with VEGFR inhibitors, significantly improving PFS, ORR, and OS vs everolimus [17].

In the RDT study patients received a cabozantinib starting dose of 100 mg daily, and dose reductions were used to manage adverse events in 59% of patients in the HCC cohort. The median average daily dose for patients in the HCC cohort was ~66 mg/day with a median time to first dose reduction of 39.5 days. Even with dose reductions, patients maintained disease control as shown by the high DCR at week 12. These data supported the choice of 60 mg daily as the starting dose for the ongoing phase 3 trial CELESTIAL.



In conclusion, cabozantinib showed preliminary signs of activity in patients with sorafenib-pretreated or sorafenib-naïve HCC. These results include observation of objective responses, a high disease control rate, and AFP responses that were independent of prior anti-VEGFR targeted therapy or ethnicity. Although the small sample size of the HCC cohort in this RDT limits interpretation of the current findings, further studies are warranted to confirm these results and further evaluate cabozantinib in HCC patients.

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